Response to Requirement for Election of Species

This addresses items 1-7 of the Action. An election of species was required on June 5, 1997 and I confirm election of species (a), that is tumors of the brain, responsive to the examiner's request at that time. The response was made with traverse. Having the benefit of seeing the current Action on the merits I believe the requirement was and is inappropriate. The claims have been searched, including claims of wider scope than those withdrawn, prior art has been cited and applied and enablement issues presented. The art-based rejections and the examiner's enablement questions are addressed (and resolved) in the discussion that follows.

Applicants disagree with the distinction between the two species in the Action as it is asserted without the benefit of scientific support or other information on which to base the alleged differences leading to patentably distinguishing species. Applicants regard their invention to include the treatment of tumors generally and that it is equally applicable to melanoma as to other cancers. Applicants thus disagree with the withdrawal of claims 23 and 35 from consideration on the basis of the present record. Reconsideration is requested.

Amendments to the Specification

Responsive the comments in item 8 of the Action, a separate section providing a brief description of the drawings has been added. The specification has been amended to refer to the underlying PCT application of which this is a national stage enter under 35 U.S.C. 371.

The specification has been amended to replace the published PCT application WO92/13943 with the serial numbers of the corresponding U.S. patent applications. The filing of a PCT application designating the United States is regarded as if filed in the United States, see 35 U.S.C. 375(a), hence incorporation by reference is proper and *In re Fouche* does not pertain. Reconsideration is requested.

An Abstract of the Disclosure based upon the underlying PCT application is attached responsive to item 9 of the Action. The examiner's comments regarding the format and content of a proper abstract are appreciated.

The Invention

The first aspect of the invention relates to the treatment of secondary metastatic tumors in the central nervous system (CNS) of a human. These tumors are tumors formed from cancer cells that have developed elsewhere in the body and have spread to the CNS, for example to the brain. They have previously been particularly difficult tumors to treat.

Secondary metastatic CNS tumors are treated in accordance with the invention by administering an effective amount of a mutant herpes simplex virus type 1 (HSV-1) which has a non-functional γ34.5 gene in each long repeat region (R_L). Each HSV-1 has two R_L regions in its genome. The mutant HSV-1 replicates in the secondary metastatic cancer cells. These cancer cells are thus selectively lysed and killed.

The second aspect of the invention concerns the treatment of cancers generally. It has been found that HSV-1 mutants which do not possess γ34.5

genes and which originate from wild-type HSV-1 strain 17 are particularly suitable for treating human cancers. Again, the HSV-1 mutants selectively replicate in, and cause the lysis and death of, the cancer cells.

First objection to the specification under 35 USC 112 first paragraph and corresponding rejection of claims 20-22, 24-34, 36-40 and 42

Reconsideration of this objection and rejection is requested. The specification does enable the invention. More particularly, the specification does provide adequate guidance on, and exemplification of the claimed methods. Reasonable correlation does exist between the scope of the claims and the scope of enablement.

The enablement of the invention must be assessed in the context of what was known by the skilled person. Prior to the present invention, viral therapy generally had been proposed for the destruction of tumors. Effects in various experimental tumor systems had been demonstrated using parvovirus H-1, Newcastle disease virus, retroviral vectors containing drug susceptibility genes, and HSV-1. Please see the titles of references 2-7 listed on pages 49 and 50 of the specification. Several of these references concerned brain tumors.

Pioneering experiments with HSV had showed a dose-dependent improvement in survival of nude mice bearing intracranial human gliomas in the brain following intratumoral therapy with mutant HSV-1 dlspTK. This virus had a deletion in the viral thymidine kinase (TK) gene and exhibited a relatively-attenuated phenotype in mice. However, dlspTK infection of tumor bearing animals caused histologically evident encephalitis.

Further, a mutant HSV-1 called R3616 with an LD_{50} (minimum dose of virus that kills 50% of infected animals) that was at least $3x10^3$ fold greater than wild type F strain virus from which it was derived, had been shown to improve the outcome of nude mice bearing intracranial human gliomas. That is the work reported in the cited paper by Markert *et al.*

Given this background and the teachings of the specification, it may be appreciated that a skilled person would require no more than routine experimentation to put the invention into practice. Suitable routes of administration and dosages are all disclosed in the specification. No scientific evidence has been cited to suggest that the present invention would not work in humans or, for that matter, in other animal models. There is a clear scientific rationale to both aspects of the present invention. No scientific papers have been cited to indicate that the underlying rationale is incorrect. Indeed, subsequent work by the inventors and others does support that rationale. Once therefore the skilled person had read the specification and understood the nature of the invention, he/she would have been able to practice the invention by applying no more than normal expertise.

Second objection to the specification under 35 USC 112, first paragraph and corresponding rejection of claims 20-22, 24-34 and 36-42.

Reconsideration of this objection and rejection is requested. The specification does enable the invention. Undue experimentation would not be required to enable the claims, even though the only strain 17 mutant mentioned in the specification is HSV-1 strain 1716. The invention does not relate to how to

obtain strains of HSV-1 which are attenuated by virtue of inactivation of the γ34.5 gene of each R_L. How to do that was taught in the prior art.

By the time of the present invention, the location of the HSV-1 γ34.5 gene in the R_L had been accurately mapped. Indeed, the γ34.5 gene had been sequenced. That knowledge would all have been available to the skilled person. It was known that inactivation of the γ34.5 gene of each HSV-1 R_L resulted in loss of neurovirulence. Techniques for achieving such inactivation had been taught in the prior art. Please see, for example, US-A-5328688 and WO 92/13943.

The specification does not therefore need to teach explicitly how to inactivate each γ34.5 gene with insertions or with smaller or larger deletions than those found in strain 1716. The specification similarly does not need to teach how to accurately predict the phenotype of mutated HSV-1. A skilled person would know how to do that from his/her own knowledge. The skilled person, on reading the specification, would therefore be able to predict that any mutant HSV-1 with non-functional γ34.5 gene would be attenuated and replicate in rapidly-dividing tumor cells but not in non-dividing cells.

<u>Third objection to the specification under 35 USC 112 first paragraph and corresponding rejection of claims 25-29 and 36-39</u>

Reconsideration of this objection and rejection is requested. The specification does enable the invention. In particular, a skilled person would know where to make deletions and, indeed, how to modify generally the γ34.5 gene of each HSV-1 R_L with the expectation of providing a virus with the phenotype of interest.

As explained immediately above, it was known in the art at the time of the present invention how to obtain strains HSV-1 that were attenuated by virtue of inactivation of the γ34.5 gene of each R_L. That does not therefore constitute the present invention. How specifically to modify each R_L BamH1 s fragment is described in WO 92/13943. Please see too US-A-5328688. A skilled person would not therefore have needed to have conducted undue experimentation in order to obtain a suitable HSV-1 strain carrying a non-functional γ34.5 gene. If he/she did not already have access to such a strain, he/she could construct one using routine expertise on the basis of the knowledge available at the time of the invention.

Rejection of claims 25-29 have and 36-39 under 35 USC second paragraph

Claims 25 and 36 have been amended to deal with this rejection.

Rejection of claims 20, 22, 24-30, 2-34 and 36-41 under 35 USC 103

New claims 20 and 30 have been limited to the features of canceled claims 21 and 31 respectively to deal with this rejection.

Information Disclosure Statement

The Official Action makes no mention of an Information Disclosure Statement included with the original application papers filed January 28, 1997. Attached is an additional copy of it in the event the original filing, made well before the first action on the merits, is not associated with the file. Copies of the documents are in my file and I will be happy to provide copies to the examiner if there are no copies in the official file. Please consider this submission and the documents identified in it during your further review of this application.

For the above reasons it is respectfully submitted the claims of this application are directed to a single invention, are properly enabled and described in the specification as filed and define subject matter fully patentable over the prior art. Reconsideration and favorable action are solicited. The examiner is encouraged to contact the undersigned should person discussions be useful to advance the prosecution of this application

Respectfully submitted,

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ABSTRACT

Use as anti-cancer agent of a mutant herpes simplex virus in which the mutant virus includes a modification in the γ34.5 gene in the long repeat region (R_L) such that the γ34.5 gene is non-functional, manufacture of medicaments and methods of testing cancer in mammals employing the HSV mutant are also described.

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